Readiness, Trust and Adherence:
Over recommended and under-researched

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Basis of Presentation

- This Presentation is based on an Article by Richard M. Grimes and Deanna E. Grimes that will appear in the Journal of the International Association of Physicians in AIDS Care.

- It may be downloaded at this time from the journal's website for a charge of $32.00.
  - So I will save you that amount of money

Expert Panels

- There are five major bodies that make recommendations with regard to treatment of HIV infected Adults
    - U.S. Depart. of Health and Human Services (DHHS)
    - International AIDS Society – USA (IAS-USA)
    - British HIV Association (BHIVA)
    - European AIDS Clinical Society (EACS)
    - World Health Organization (WHO)

Expert Panels

- The expert panels make evidence based recommendations for HIV treatment.
- They also give evidence based advice for treatment of patients with:
  - Pregnancy,
  - HIV-associated nephropathy,
  - HBV co-infection and Hepatitis C co-infection,
  - Tuberculosis and
  - Cardiovascular disease.

Expert Panels

- The DHHS, EACS, WHO and IAS-USA expert panels use a Scale for identifying the strength of their recommendations

- For, Example, DHHS uses:
    - A: Strong recommendation for the statement
    - B: Moderate recommendation for the statement
    - C: Optional recommendation for the statement

Expert Panels

- DHHS guidelines also qualify its recommendations with strength of evidence ratings:
  - I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
  - II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
  - III: Expert opinion

Expert Panels

- These panels also make recommendations with regard to:
  - Readiness,
  - Trust and
  - Adherence.
- The panels do not provide any ratings of:
  - Strength of their recommendations
  - Strength of the evidence

Our Study

- Purpose: Examine the strength of the evidence supporting the recommendations regarding readiness, trust and adherence.

- Method: Examined three review papers published in 2010.

  – When a referenced article in one of the reviews was particularly pertinent we reviewed that paper.

The review papers – Readiness and Trust.

Grimes RM, Grimes DE. Readiness: The State of the Science (or the Lack Thereof). Curr HIV/AIDS Rep. 2010 ;7(4):245-52.

Graham JL, Giordano TP, Grimes RM, et al. Influence of trust on HIV diagnosis and care practices: A literature review. J Internat Assoc Physicians AIDS Car. 2010;9(6):346-52.

The Review Papers - Adherence

Simoni JM, Amico KR, Smith L, et al. Curr HIV/AIDS Rep 2010;7:44-51.

Simoni JM, Kurth AE. AIDS Behav. 2006;10(3):227-245.

Simoni JM, Pearson CR, Pantalone DW, et al.. J Acquir Immune DeficSyndr. 2006;43(suppl 1):S23-S35.

Expert Panel Recommendations On Readiness

- DHHS says "Prior to writing the first prescriptions, the clinician should assess the patient's readiness to take medication"

- IAS-USA says ""Patient readiness for treatment is a key consideration when deciding when to initiate ART."

- BHIVA guidelines state that patients who have CD4 counts between 200 and 350 should only be started if they are "ready."

Expert Panel Recommendations On Readiness

- None of these panels provide any guidance on how to determine readiness.
  - DHHS has a blank space in the table of how to implement its recommendations
  - IAS-USA makes its strong statement in the abstract of the article but then does not ever discuss it again.
  - BHIVA provides no guidance on how to determine readiness.

Expert Panel Recommendations On Readiness

- The EACS And WHO each provide a series of questions to ask to determine patient readiness.

    - Neither group provides any guidance how to use the questions to predict adherence. Particularly in an individual patient.

Readiness – The Need

- Clinicians need a tool that sorts the "ready" from the "unready" that is both sensitive and specific.

  - It correctly identifies those who are ready to start ART and also correctly identifies those who are not ready to start.

Why sensitive and Specific?

Failing to start ART in those who are judged "unready" but are "ready" may lead to unrecoverable deterioration of the immune system.

Starting those who are judged "ready" but are not ready may lead to"

- Drug resistant virus
- Future treatments will be more costly

Readiness – The evidence

- We asked 83 Patients to assess their reactions to finding out HIV status.

- We then asked them to say how long until they thought they were ready for ART.

Times until ready to start	Percent of patients
Immediately	42%
Less than 1 year	46%
More than one year	12%

Morgenstern TT, Grimes DE, Grimes RM
HIV Clin Trial 2002;3:168-72

Readiness- The Evidence

There were relationships between readiness and:

- Anger p = .06
- Hopelessness p = .02
- Anxiety p = .03
- Confusion p = .03
- Denial p = .01

- Morgenstern TT, Grimes DE, Grimes RM. HIV Clinical Trials 2002;3:168-72

Readiness – The evidence

- Thought we were on to something.
  - If patients could retrospectively say whether they were ready or not, then maybe they could also say it prospectively.
  - Also readiness might be related to a prospective measurement of a psychological state

Readiness – The evidence

- Our next Study
  - 24 patients starting therapy
  - 15 restarting therapy after a break of > 6 months under the assumption that experienced patients would be better judges of their readiness.

Grimes RM, Grimes DE. J Internation Association of Physicians in AIDS Care. 2009;8:364-6.

Readiness – The Evidence

Given psychological tests to see if the scales would predict adherence over 5 months

Also asked to state their readiness to start HAART.

- Measured readiness by a Likert scale and a visual analog scale.
- Measured Adherence by prescription renewals.

Readiness – The evidence

- Results:
  - No psychological scale correlated with readiness or adherence at the R = < .10 level (all were not statistically significant)
  - Neither of two measure of self assessed readiness correlated with adherence.

Grimes RM, Grimes DE. J international Assn of Physicians in AIDS CARE 2009;8:364-6

Readiness – The evidence

- We could not do it so maybe others could.

- Reviewed the literature and found:
  - 27 articles relating to readiness to initiate HAART
  - 18 articles did not relate readiness to adherence.

Grimes RM, Grimes DE Current HIV reports
2010;7:245-52.

Readiness – The evidence

- Of nine articles relating readiness to adherence:
  - Follow up periods were one mo. (3), 5-9 weeks, 16 weeks, 5 mos., 6mos., 1 year (2) ,
  - No measure was sensitive or specific.
  - One showed promise but failed in follow up study.

Readiness – The evidence

- No measure of readiness that predicts future adherence and the idea may not make sense.
  - "Believing that a readiness measure that makes a prediction for a person starting HAART in 2010 will be able to predict the patient's adherence behavior in 2012 or 2020 seems like a demand for a crystal ball rather than a psychometric instrument."
  - A silly idea for lifelong therapy.

Expert Panel Recommendations on Trust

- DHHS guidelines emphasize the importance of maintaining a trust relationship between the patient and his/her physician.
  - "Coercive and punitive policies undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize maternal, fetal, and neonatal well-being."
  - "Establishing a trusting relationship over time and maintaining good communication will help to improve adherence and long-term outcomes."

Expert Panel Recommendations on Trust

- EACS says that tust is an important step in establishing readiness
  - "Show respect for patient attitude / Try to understand health and therapy beliefs / **Establish trust** / Provide individualized short information. "

Trust – The Need

- If having a trust relationship is necessary there must be some way of:
  - Establishing whether it exists
  - Finding a way of causing it to occur if it does not exist.
  - Having a means of maintaining it.

Trust – The Evidence

- James Graham of Legacy Community Health Services in Houston reviewed the literature on trust in general and specifically for HIV care.

- He found 38 articles dealing with trust.

Graham JL, Giordano TP, Grimes RM, et al. J Internat Assoc Physicians AIDS Car. 2010;9(6):346-52.

Trust – The evidence

- Graham et al. found:
  - No agreement on the definition of trust.
  - Trust scales had been developed for physicians, nurses, pharmacists, the Health care system in general, particular health systems (e.g. a HMO)
  - Almost as many trust scales as trust researchers

- Graham JL, Giordano TP, Grimes RM, et al. J Internat Assoc Physicians AIDS Car. 2010;9(6):346-52.

Trust – The Evidence

- Most trust studies have looked at who is trustful or not trustful.
  - Particularly examined trust of African-Americans vs. White Americans.
  - Also looked at trust in patients with certain medical conditions – e.g. Lupus, arthritis.

Graham JL , Giordano TP, Grimes RM, et al. J Internat Assoc PhysiciAIDS Car. 2010;9(6):346-52.

Trust – The Evidence

- Found 13 studies on trust in HIV patients.
  - Eight articles on Trust levels in minorities
    - Houston study showed conspiracy belief did not impact time of entry to care or adherence.
  - Three articles on whether lack of trust explains why minorities are underrepresented in clinical trials. (Answer seems to be no impact)
  - Two studies looking at whether trust levels affected care.

Clark A, Mayben JK, Harman C et al. Aids
Pat Car STDs. 2008;22:753-9

Trust – The Evidence

- Studies examining trust's impact on care.
  - One study[1] showed patients losing trust were more likely to change regimens and to have HIV or HAART related events
    - Not clear which way is causality
    - Patient who lost trust were shown to regain it.
  - Graham study[2] showed trust had no impact on time to entry to care but was associated with care retention

1. Preau M, Le Port C, Villes V, et al. JAIDS 2008;47:467-71. 2. Graham J, Grimes R, Giordano T et al. Abstracts of 18th International AIDS conference. Vienna, Austria July 18-23, 2010.

Trust – The Evidence Conclusion

- There is no evidence that there is a sensitive and/or specific measure of Trust

- Currently available measures have weakly predicted outcomes of HIV care in a single study.

- There have been no studies that used a trust scale to predict adherence.

Trust Conclusion

- Can you ask people who do not trust you to honestly answer that they do not trust you because you say "trust me, you can honestly answer these questions"?

Question

- Do readiness scales fail to predict adherence because readiness scales are bad or because adherence measures are bad?

Question??

- Important question because guidelines say that clinicians should assess adherence.
  - All but one of the guidelines fail to say how this assessment should be done.
  - No guideline says how to improve it if it is lacking.

Adherence – The Recommendations

- All of the Guidelines recommend assessing adherence.

- Only the EACS gives direction on how to assess adherence.

Adherence – The Recommendations

- The EACS says that adherence can be assessed by asking two questions.
  - "In the past 4 wks how often have you missed a dose of your HIV medication: everyday, more than once a wk, once a wk, once every 2 wks, once a month, never?"
  - "Have you missed more than one dose in a row?"

Adherence – The Recommendations

- Swiss study (n = 2664) of suppressed patients that showed that patients who reported missing in last 4 weeks:
  - 2 doses were 2.17 times more likely to rebound to >500 copies than those reporting perfect adherence.
  - > 2 doses were 3.66 times more likely to rebound
  - Sensitivity and specificity not given
  - Utility of the 2nd question was not reported.

Correctly Assessing Adherence is Important

- Poor adherence is linked to:
  - Virologic failure
  - Decline in immune function
  - Requiring more expensive regimens
  - Loss of treatment options.
  - Opportunistic disease
  - Hospitalization and death

Adherence – The Evidence

- A Search of Medline using medication adherence and HIV or AIDS as search terms found:

  - 789 articles with those terms were published between January 1, 2008 and October 12, 2012.

- We either know an enormous amount about Adherence or we know nothing.

Adherence – The Evidence

- How has adherence been most commonly measured, non-clinically?
  - Patient report at clinic visits or regular phone calls
  - Pharmacy renewal records
  - Pill counts-unannounced and at clinic visits
  - Electronic recording devices

Adherence – The Evidence

- Other non-clinical ways of measuring adherence
  - Patient medication diaries
  - Clinician assessment
  - Directly observed therapy

Adherence – The Evidence

– HIV Laboratory markers (e.g. viral load and CD4 count)

– Blood/urine levels of drugs

– Disease progression

Adherence – The Evidence
Patient Report

- Simoni reported on 77 studies done between 1996 to 2004 using self report as a measure of adherence.

  – Recall times were 1,2,3,4,7, 14, 28 and 30 days as well as 1,3 and 6 months.

  – Sample sizes ranged from 26 to 2528

Simoni J, Kurth AE, Pearson AR et al AIDS Behav.2006;10:227-245

Adherence – The Evidence Patient Report

- Simoni et al. found that most correlated self report of adherence with:
  - Viral Loads and CD4 counts
  - Usually found some relationship but not clinically useful
    - Only two reported sensitivity and specificity.

Adherence – The Evidence
Pill Counts

- Simoni found Correlations between pill counts and self report in 5 studies
  - r values were .85,.76,.62,.89 and one study showed a non-significant relationship.

Adherence – The Evidence
Pill Counts

- Pill counts are easily gamed by patients willing to please.
  - Consists of bringing pill bottles to clinic.
    - Secret stashes, empty bottle before bringing to clinic, lost bottle, etc.
  - Unannounced visits
    - Hide pills when fail to take, empty bottle when observer shows up, etc.

Adherence – The Evidence Electronic Monitoring

Adherence – The Evidence Electronic Monitoring

Adherence – The Evidence Electronic Monitoring

- Records when pill container is opened
  - Simoni reported that it correlated with self report at r = .49,.38,.47,.38,.40,.87,.34,.63 and one report of not significant.
- Does not account for removing extra doses for later when opening the bottle.
- Opening does not ensure taking.

Adherence – The Evidence Pharmacy Refills

- Logical measure of non-adherence – you cannot take the pills unless you have them.

- Simoni found that they correlated with self report at r = .82,.62,.19

Adherence – The Evidence Pharmacy Refills

- A Houston study at Thomas Street Health Center found that filled Rxs are not picked up by some patients
  - Patients, who had ordered Rxs that they did not pick up, had adherence reduced from 58% to 36% with picked up vs. filled Rxs
  - Note: adherence is not that bad at TSHC but patients were those not picking up meds.

Adherence – The Evidence

- When multiple measures are use on the same patients for the same time period they correlate poorly. For, example:
  - Golin found that self report correlated with electronic monitoring at r= .36 and with pill count at r = .46. Electronic monitoring correlated with pill count at r = .62

Golin CE, Liu H, Hays RD et al. J Gen Intern Med. 2002;17:756-65

Adherence – The Evidence

- Holzemer et al used five measures on Thomas Street patients and the average correlation was r = .07.

Holzemer W, Bakken S, Portillo CJ, Grimes R., Et al. Nur Res. 2006;55:189-97

Adherence – The Evidence

- Assessing the commonly used measures of adherence
  - No measure have been proven to be superior to any other measure .
  - No measure has been shown to predict clinical outcomes in a fashion that is any better than another measure.

Adherence – The Evidence Necessary Level of Adherence

- Established et al. at 95% by Paterson in a 2000 publication which has been referenced over 600 times in Medline.
  - Based on 81 patients followed for as little as 3 months or as long as 18 months.
  - Only monitored one of 3 drugs being taken.
  - Used drugs that are no longer being used because of their short half life

Adherence – The Evidence Necessary Level of Adherence

- Other often quoted studies are:
  - Bangsberg et al. with 76 patients in 1998-9
  - Lima et al with 903 patients in 2000-2004.
  - These and other studies compare < 95% with > 95% and show that > 95% is better.
- No studies of the necessary level of adherence using modern therapies has been published.

Adherence - The Evidence

- No studies of patterns of non-adherence
  - Current research assumes that all 95% adherence is the same.
- 5% non-adherence means missing < 19 dose in a year for a one per day regimen
  - Could be 1-2 per month, 18 consecutive days, every other day for 36 days, etc.

Adherence – The Evidence

- To summarize
  - There is no agreed upon measure of adherence as all have significant flaws
  - Measures do not correlate with each other.
  - The level of adherence for modern therapies has not been established
  - The effect of patterns of non-adherence have not been investigated

Can Interventions Improve Adherence?

- Methods used to improve adherence
  - Cognitive behavioral therapy,
  - Motivational interviewing,
  - Medication management strategies
  - Group Counseling
  - Individual counseling sessions.

Can Interventions Improve Adherence?

- The interventions ranged from single sessions to over 50 sessions
- The number of sessions ranged from a single one hour session to multiple sessions lasting 15 months.
- Individual sessions lasted from 45 minutes to 2.5 hours.
- Sample sizes ranged from 10 to nearly 1000.
  - Most had fewer than 100 patients.

  - Simoni JM, Amico KR, Smith L, et al. Curr HIV/AIDS Rep 2010;7:44-51.

Can Interventions Improve Adherence?

- Individuals delivering the interventions:
    - Lay individuals, e.g. peer counselors
    - Counselors,
    - Social workers,
    - Psychologists,
    - Nurses,
    - Pharmacists
    - Physicians.

Can Interventions Improve Adherence?

- The Populations that were studied included
  - ART naïve patients,
  - Patients who had previous difficulty adhering,
  - Women,
  - Minorities
  - ART experienced patients.

Can Interventions Improve Adherence?

- Adherence has been measured by:
  - Electronic monitoring, Pill counts, Medication diaries, Patient self-report, Provider report, Clinic Records, and Pharmacy records.

And, we know that they do not correlate with one another

Can Interventions Improve Adherence?

- Rueda et al. reviewed the evidence of the effectiveness of 43 adherence interventions
  - The patient populations ranged in size from 22 to 966.
  - Only 53% of the studies showed a positive effect on adherence.
  - Of the twenty studies showing a positive impact that also measured virologic or immunologic outcomes, only seven (35%) improved the biological outcome.

Can Interventions Improve Adherence? - Summary

– Studies have used multiple approaches for varying lengths of time, on different populations, in multiple venues using different measures of adherence

– The interventions seldom had an impact on whatever measure of adherence is used or on patient outcomes.

– No study replicated a previous study.

Can Interventions Improve Adherence?

- Centers for Disease Control that lists "good" evidence based interventions for antiretroviral therapy interventions.

- Lists eight studies

- Two used directly observed therapy

- One used a pager to remind patients

- Five involved teaching/counseling sessions

Can Interventions Improve Adherence?

- In CDC's listed intervention using the pager to remind patients and to send health messages, the study found
  - No significant positive intervention effect on medication adherence behaviors

Can Interventions Improve Adherence?

- In CDC's listed interventions using directly observed therapy:

  - One study showed that 16% more patients were likely to achieve an undetectable viral load or a 1 log drop in viral load.

  - The other study showed that 71% of the directly observed therapy patients were undetectable at 6 months versus 46% of the control group.

Can Interventions Improve Adherence?

- In CDC's listed as "good" studies Five involved teaching/counseling sessions
  - Nurse made 24 home visits in year. No statistically significant change in CD4 count or viral load.
  - 5 sessions at the clinic totaling 10 hours over 6 months and 5 phone calls in 8 weeks. Adherence was 46% vs. 28% in the control group.

Can Interventions Improve Adherence?

- 6 sessions over six months that totaled 11 hours
  - There was improvement in adherence during 6 months but declined afterward.
- Serodiscordant couples study used four 45- to 60-minute sessions over 5 weeks.
  - Adherence was 76% vs. 60% in controls
  - Differences not significant by nine months

Can Interventions Improve Adherence?

- In CDC's listed as "good" studies, there was one study that used posters, flyers and brochures to inform patients of the importance of adherence

- Also gave training providers on how to give a 3-5 minute patient talk on adherence to give the talk at every visit.

  - At 11-18 months follow up intervention group had 86% adherence vs. 70% in control group.

Can Interventions Improve Adherence?

- In Summary CDC's "good' intervention studies showed:
  - Four highly impractical counseling/education sessions had only small effect on (~15%) effect on adherence
  - Two, unlikely-to-be implemented-in-the-real-world, directly observed therapy studies had one with significant impact on adherence .
  - A pager based study showed no improvement.

Can Interventions Improve Adherence?

- The study of what you can achieve using clinician training is intriguing.
  - It did as well as the expensive, unsustainable, major interventions.
  - Very cheap
  - Is the only intervention that is likely to implemented for the next 30-40 years.
    - People will continue to be seen in the clinic

Can Interventions Improve Adherence?

- WHO THE HELL KNOWS?

- BUT WHATEVER IT IS, IT WILL HAVE TO BE CLINIC BASED AND CHEAP!

- NEEDS A VERY LONG TIME HORIZON.

- PREVIOUS STUDIES GIVE NO GUIDANCE.

Why is the State of the Science So Poor?

- There has been nothing to build upon
  - Other conditions/medications (e.g. statins, antihypertensives) have been as poorly studied.
  - This is really Hard to do.
  - There is no funding for this

Why is the State of the Science So Poor?

—Nobody owns readiness, trust and adherence

- NIDA funds adherence in drug abusers
- NCI might fund adherence in cancer treatment
- NHLBI might fund statin adherence
- Etc.

Why is the State of the Science So poor?

- Experts in the field act as if it is easy and/or solved
  - Guidelines are, at best, cavalier in their treatment of these unsolved issues.
  - The holy grail of 95% adherence is never challenged
  - Researchers do not build on each others efforts.

Conclusion

- Whatever you are doing to improve readiness, trust and adherence, has as much evidence to support it as any other method that you might use.